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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/403,882	03/20/00	FARINAS J	UCSF1100-3

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EXAMINER	
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ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/403,882	Applicant(s) FARINAS, JAVIER	
	Examiner " Neon" Phuong Huynh	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 February 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-63* is/are pending in the application.

4a) Of the above claim(s) *19-59,61 and 62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18,60 and 63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. Preliminary amendment, filed 2/21/01, is acknowledged. Specification has been amended.

2. Claims 1-63 are pending.

3. Applicant's election with traverse of Group I claims 1-18, 60 and 63, filed 2/21/01, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

4. Claims 19-59 and 61-62 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

5. Claims 1-18, 60 and 63 are being acted upon in this Office Action.

6. The drawings, filed 3/20/00, are approved.

7. The disclosure is objected to because of the following informalities: (1) the use of the trademark "BIODIPY" has been noted in this application. It should be capitalized or accompanied by the ™ or ® symbol wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. Appropriate correction is required.

8. Applicant's provision of domestic priority documents 60/081,118 filed 4/8/1998 and 60/018,340, filed 5/17/1996 is acknowledged. However, the provisional Application 60/018,340, filed 5/17/1996, appears to be incorrect. Applicant is invited to point to the suppose error of Provisional Application number 60/018,340. Correction in the Declaration is required.

9. Applicant should amend the first line of the specification to reflect the relationship of instant application to priority documents PCT US99/07847.

10. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The claims encompass a method for localizing a probe comprising a cell expressing a single chain antibody with a probe/ligand conjugate wherein said single chain antibody has "substantial identity" to SEQ ID NO: 1 and said single chain antibody is an "homologue of SEQ ID NO: 1".

The specification as filed discloses only one single chain antibody represented by polynucleotide of SEQ ID NO: 1 (See Sequence Listing). The specification further defines the term "homologue" as two sequences or parts thereof that are greater than or equal to 75% identical when optimally aligned using ALIGN program (See page 11, line 11).

However, the specification does not reasonably provide a **written description** of *any* homologue of SEQ ID NO: 1 that has sequence identity greater than or equal to 75% of SEQ ID NO: 1 other than SEQ ID NO: 1.

Besides the polynucleotide of SEQ ID NO: 1 that encodes for a single chain antibody, Applicant has not disclosed sufficient species of "homologue" of polynucleotide sequence that is at least 75% identical to SEQ ID NO: 1 such that one skilled in the art would conclude that applicant was in possession of the claimed method comprising a single chain antibody that has "substantially identity" to SEQ ID NO: 1. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *see University of California v. Eli Lilly and Co. 43 USPQ2d 1398.* Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description"

Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

14. Claims 1-3, 5, 11, 13, 14 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite in the recitation of "a)" and "1), 2) and 3)". As written, it is unclear dependent claims depend on claim 1, 2, 3 or sub 1, 2, 3. It is suggested that applicant use Markush language to include functional limitation in the claim. See MPEP 2173.05.

The phrase "as in any" as recited in claim 63 is indefinite and ambiguous. It is suggested that claim 63 be recited to depend on claim 60.

Claim 5 is indefinite in the recitation of "substantial identity" as defined on page 13 of the specification that polynucleotide sequence comprises a sequence that has at least 30 percent sequence identity, at least 60 percent sequence identity. As written, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

The phrase "said cell" as recited in claims 11, 13, 14 and 15 have no antecedent basis in base claim 3. Base claim 3 recites probe or ligand conjugate.

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –
(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

16. Claims 1-6, 8, 12-14 and 16-17 are rejected under 35 U.S.C. 102(e) as being anticipated by Chestnut *et al.* (US Pat No. 6,017,754, filed Aug 1995, PTO 892).

Chestnut *et al* teach a method of identifying and selecting a cell to study genes of interest at a cellular level by transfecting eukaryotic or mammalian cells with plasmids that encode a single chain antibody (sFv) directed against phOx wherein said single chain antibody is a homologue of SEQ ID NO: 1 and has substantial identity to SEQ ID NO: 1 of instant application

(See Fig 1A-2, Fig 6, column 1, line 54 bridging column 2 line 1, column 6, line 11, in particular). The said cell expresses a single chain antibody (anti-phOx) which is a specific binding partner or receptor for the phOx ligand (See column 2, Summary of Invention, column 6, line 13, column 6, line 41, in particular). The said single chain antibody comprises a fusion protein that is engineered to include coding sequence for a transmembrane domain of the human platelet derived growth factor receptor (PDGFR) or any membrane anchoring sequence so that when expressed in transfected cells, this fusion protein is anchored to the membrane via the transmembrane domain of the PDGFR (See column 10, line 4-26, in particular). The reference further teaches that the use of a single-chained antibody (rAB) is advantageous because the smaller size of the single chain coding sequence allows other inserted coding sequence to be longer without losing cloning efficiency since cloning efficiency is inversely related to vector size (See column 10, line 27-31, in particular). Chestnut et al further teach that the hapten (PhOx) as the ligand can be conjugated to a fluorescent (FITC) spectroscopic probe or other labeled via a linker moiety (PhOx-BSA-FITC) to allow for identification and selection of the transfected cell shortly after transfection by detecting fluorescence emission which is one of the optical properties of the FITC probe (See column 7, line 8-13, in particular). The said ligand (PhOx) binds to the specific binding partner (anti-PhOx antibody or receptor) non-covalently. Thus, the reference teachings anticipate the claimed invention.

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. Claims 1-3, 7, 11, 15, 60 and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chestnut *et al.* (US Pat No. 6,017,754, filed Aug 1995, PTO 892) in view of Haugland *et al* (Handbook of Fluorescent Probes and Research Chemicals 6th edition, 1996, pages 13-15, 18-19; PTO 892) or Rizzuto et al, Current Biology 5(6): 635-642, 1995; PTO 892).

The teachings of the '754 patent have been discussed supra.

The claimed invention as recited in claims 7, 11, 15, 60 and 63 differs from the reference wherein probe/ligand conjugate is membrane permeant, adding a stimulus to said cell and detecting said probe/ligand conjugate before and after addition of stimulus.

Haugland *et al* teach spectroscopic probes including BODIPY FL, fluorescein, rhodamine, tetramethylrhodamine (See page 13-14, in particular). Haugland *et al* further teach BODIPY FL as a fluorescein substitute with excitation/emission maxima at 503 and 512 nm, respectively. The reference further teaches that BODIPY conjugates tend to be more membrane permeant to live cells than are conjugates of charged fluorophores (See page 14, column 2, in particular). The advantages of BODIPY FL are: (1) the spectra are insensitive to solvent polarity and pH; (2) the narrow emission bandwidth improves peak intensity over that of fluorescein; (3) little or no spectral overlap with longer wavelength dyes such as tetramethylrhodamine; and (4) greater photostability than fluorescein (See page 256, Fig 1, page 262, column 2, in particular). Haugland *et al* further teach a method of linking the BODIPY FL dye to various proteins, nucleotides (See page 15, in particular). Further, the fluorescent moiety is detected by confocal laser scanning microscopy, fluorescence microscope or flow cytometry application (fluorescence activated cell sorting) which all measure the fluorescence emission, the optical property of the probe (See page 19, in particular).

Rizzuto *et al* teach a method of using recombinant green fluorescent protein (GFP) of *Aequorea victoria* as a tool for visualizing subcellular organelles in living cells. Rizzuto *et al* further teach a method of making plasmid encoding recombinant GFP, hemagglutinin HA1 epitope (membrane bound), and subunit VIII of cytochome c (mitochondria membrane) and expressing these proteins as a fusion protein in mammalian cells (HeLa cells) (See page 636, GFP cDNA construct, in particular). The expression of recombinant GFP in HeLa cells is visualized by fluorescence microscope or confocal microscope (See page 637, 639, in particular). The reference further teaches adding a stimulus (noradrenaline and histamine) to said cell and detecting the GFP conjugate before and after addition of said stimulus (See page 639-640, Use of GFP in physiological experiments, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute BIODIPY FL taught by Haugland *et al* or GFP taught by Rizzuto *et al* with the fluorecein (FITC) conjugated to the phOx ligand as taught by Chestnut *et al* for a method of localizing a probe in a cell expressing said probe. One would have been motivated, with a reasonable expectation of success, to substitute BIODIPY FL taught by

Haugland *et al* because the advantages of BODIPY FL are: (1) the spectra are insensitive to solvent polarity and pH; (2) the narrow emission bandwidth improves peak intensity over that of fluorescein; (3) little or no spectral overlap with longer wavelength dyes such as tetramethylrhodamine; (4) greater photostability than fluorescein (See page 256, Fig 1, page 262, column 2, in particular); (5) BIODIPY FL is membrane permeant to live cells (See page 14, column 2, in particular). One would have been motivated to use the plasmid that encodes a single chain antibody (sFv) directed against phOx as taught by Chestnut *et al* because the smaller size of the single chain coding sequence allows other inserted coding sequence to be longer without losing cloning efficiency since cloning efficiency is inversely to vector size (See column 10, line 27-31, in particular) and the additional advantage of using antibody binding domain is that it has a higher level of specific binding and less cross-reactivity with irrelevant molecules as taught by Chestnut *et al* (See column 6, line 26-33, in particular). One would have been motivated, with a reasonable expectation of success, to substitute green fluorescent protein taught by Fizzuto *et al* for the fluorecein (FITC) conjugated to the phOx ligand as taught by Chestnut *et al* for a method of visualizing subcellular organelles in living cells because GFP conjugate can be targeted to virtually any intracellular organelle with no effect on the light emission properties or the spectral properties of the fluorescent protein and it provides a tool for monitoring stimulus under physiological experiments at the single-cell level as taught by Rizzuto et al (See page 641, in particular).

19. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chestnut *et al.* (US Pat No. 6,017,754, filed Aug 1995, PTO 892) in view of Haugland *et al* (Handbook of Fluorescent Probes and Research Chemicals 6th edition, 1996, pages 13-15, 18-19; PTO 892) as applied to claims 1-3, 7, 11, 15, 60 and 63 and further in view of Lauffer et al (U. S. Pat No. 5,628,982, May 1997; PTO 892).

The combined teachings of Chestnut and Haugland have been discussed supra.

The claimed invention in claim 9 differs from the references only by the recitation of said detecting is by means of NMR imaging.

The '982 patent teaches hydroxyl-aryl metal chelates as NMR contrast agents or probes for diagnostic NMR imaging. By incorporating 2-hydroxy-aryl groups into the metal chelating ligand, the metal ion chelate NMR contrast agents (ligands) are produced which preferentially bind to specific proteins (the binding partners) in a non-covalent manner and hence the binding of

the affinity of the metal chelate to the protein or distribution is enhanced (See column 1, Summary of Invention, column 15, line 38, in particular). The advantages of gadolinium ion with seven unpaired electrons are: (1) it can be used with a chelating agent having a number of open sites; (2) it can act as a contrast agent at very low dosages; (3) it can be no more toxic than iron used with a chelating agent having no open sites as taught by the '892 patent (See column 15, line 29-34, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute hydroxy-aryl metal chelates as NMR contrast agents taught by the '982 patent with the BIODIPY FL probe taught by Haugland *et al* or the fluorecein (FITC) probe conjugated to the phOx ligand as taught by Chestnut *et al* for NMR imaging as taught by the '982. One would have been motivated, with a reasonable expectation of success, to substitute hydroxy-aryl metal chelates as NMR contrast agents taught by the '982 patent for NMR imaging because the gadolinium ion with seven unpaired electrons can be used with any chelating agent having a number of open sites; it can act as a contrast agent at very low dosages and be no more toxic than iron used with a chelating agent having no open sites as taught by the '892 patent (See column 15, line 29-34, in particular).

20. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chestnut *et al.* (US Pat No. 6,017,754, filed Aug 1995, PTO 892) in view of Haugland *et al* (Handbook of Fluorescent Probes and Research Chemicals 6th edition, 1996, pages 13-15, 18-19; PTO 892) as applied to claims 1-3, 7, 11, 15, 60 and 63 and further in view of Green et al (U.S. Pat No. 5,324,502, June 1994; PTO 892).

The combined teachings of Chestnut and Haugland have been discussed supra.

The claimed invention in claim 10 differs from the references only by the recitation of said detecting by positron emission tomography, respectively.

The '502 patent teaches radiopharamceutical for positron emission tomography (PET) wherein said radiopharmaceutical is positron emitting gallium-68(III) cationic complex or lipophilic complex which is membrane permeant due to its lipophilic content. The said radiopharmaceutical has the properties of prolonged retention in the targeted tissue relative to the blood levels and relative to radiopharmaceutical concentration in the adjacent non-targeted tissues (See column 1, line 61-66, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the positron emitting gallium-68(III) cationic complex or lipophilic complex taught by the '502 patent with the BIODIPY FL probe taught by Haugland *et al* or the fluorecein (FITC) probe conjugated to the phOx ligand as taught by Chestnut *et al* for PET as taught by the '502. One would have been motivated, with a reasonable expectation of success, to substitute the radionuclide taught by the '502 patent for PET because of its biodistribution properties where the retention of the radionuclide (probe) is prolonged in the targeted tissue relative to the blood levels and relative to radiopharmaceutical concentration in the adjacent non-targeted tissues as taught by the '502 patent (See column 1, line 61-66, in particular).

21. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chestnut *et al.* (US Pat No. 6,017,754, filed Aug 1995, PTO 892) in view of Haugland *et al* (Handbook of Fluorescent Probes and Research Chemicals 6th edition, 1996, pages 13-15, 18-19; PTO 892) as applied to claims 1-3, 7, 11, 15, 60 and 63 and further in view of Youn *et al* Analytical Biochemistry 232: 24-30, 1995; PTO 892).

The combined teachings of Chestnut and Haugland have been discussed supra.

The combined teachings differ from the claimed invention by measuring one of the optical properties of the probe by fluorescence anisotropy.

Youn *et al.* teach the use of fluorescence energy transfer immunoassay (FRET) based on the use of a ruthenium metal ligand complex. In this assay, the human serum albumin (the ligand) is covalently labeled with the donor [Ru(bpy)2(phen-ITC)]2+ and the anti-human serum albumin antibody (the receptor) is labeled with the acceptor reactive Blue 4. Upon binding of the acceptor-labeled antibody (specific binding partner) to the Ru-labeled antigen (ligand), the intensity and decay time of ruthenium metal ligand complex decrease while the anisotropy increases (See page 25, column 2, page 27, Figs 3 & 4, Table 1, in particular). One of the advantages of the Ru complex is its long decay time; since it is chemically and photochemically stable, it allows off-gating of the interfering autofluorescence and thereby increases the sensitivity of the time-resolved immunoassays. The FRET assay is more reliable because the decay times of the Ru complex are mostly independent of the overall intensity of the emission. Finally, the long decay time of the Ru complexes can be measured with simple instrumentation, and allow the measurement of rotational correlation times up to 1 μs (See page 24-25, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the ruthenium metal ligand complex probe taught by Youn *et al* with the BIODIPY FL probe taught by Haugland *et al* or the fluorecein (FITC) probe conjugated to the phOx ligand as taught by Chestnut *et al* for a FRET assay as taught by Youn *et al*. One would have been motivated, with a reasonable expectation of success, to substitute the ruthenium metal ligand complex taught by Youn *et al* because the Ru complex is its long decay time, chemically and photochemically stable which allows off-gating of the interfering autofluorescence and thereby increases the sensitivity of the time-resolved immunoassays. One would have been motivated, with a reasonable expectation of success, to substitute the ruthenium metal ligand complex taught by Youn *et al* for The FRET assay because it is more reliable since the decay times of the Ru complex are mostly independent of the overall intensity of the emission and the long decay time of the Ru complexes can be measured with simple instrumentation as taught by Youn et al (See pages 24-25 and 29, in particular).

22. No claim is allowed.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

24. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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